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(81) Designated States (unless otherwise indicated, for every  
kind of national protection available): AE, AG, AL, AM,  
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,  
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,  
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,  
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,  
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PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,  
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kind of regional protection available): ARIPO (BW, GH,  
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
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GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK,  
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,  
ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**

— as to the identity of the inventor (Rule 4.17(i)) for all des-  
ignations

— as to applicant's entitlement to apply for and be granted  
a patent (Rule 4.17(ii)) for the following designations AE,  
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ,  
CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE,  
EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,  
JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,  
MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM,  
PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ,  
TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM,  
ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD,  
SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY,  
KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG,  
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT,  
LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF,  
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,  
TD, TG)

— as to the applicant's entitlement to claim the priority of the  
earlier application (Rule 4.17(iii)) for all designations

— of inventorship (Rule 4.17(iv)) for US only

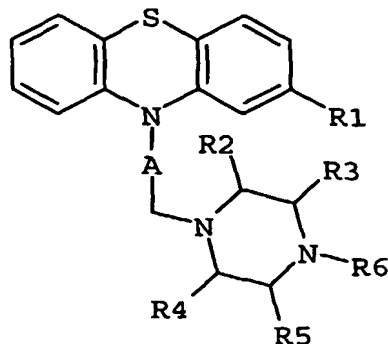
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[Continued on next page]

(54) Title: **USE OF PIPERAZINE PHENOTHIAZINE DERIVATIVES IN THE MANUFACTURE OF A MEDICAMENT WITH  
NEUROPROTECTOR AND/OR NEUROTROPHIC EFFECTS ON CNS AND/OR PNS**



(I)

(57) Abstract: This invention relates to a new use of piper-  
azinephenothiazine derivatives and their pharmaceutically acceptable  
salts or esters in the manufacture of a medicament with neuroprotector  
and/or neurotrophic effects on CNS and/or PNS. The piperazine  
phenothiazine derivatives are selected from compounds of formula (I)  
wherein A represents a straight or branched alkylene chain of from 2 to  
6 carbon atoms separating the nitrogen atoms linked thereto by at least  
two carbon atoms; R1 represents hydrogen, halogen, lower alkyl, lower  
alkoxy, lower alkanoyl, lower alkyl-mercapto, trifluoromethylmercapto,  
lower alkyl-sulfonyl (preferably methylsulfonyl), perfluoroalkyl of 1  
to 3 carbon atoms; R2, R3, R4 and R5 each represent methyl, ethyl or  
hydrogen, R6 represents hydrogen, lower alkyl, hydroxy-lower-alkyl or  
aliphatic acyloxy-lower-alkyl having 1 to 4 carbon atoms in the acyloxy  
portion and 1 to 6 carbon atoms in the alkyl portion, CH<sub>2</sub>-CH<sub>2</sub>-O-R7  
where R7 represents hydrogen, COR8 where R8 is a branched or straight chain alkyl radical of from seven to fourteen carbon atoms.



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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP2004/005183

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K31/5415 A61P25/28 A61P25/16 A61P25/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE, WPI Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HALE M S ET AL: "LOW DOSE PERPHENAZINE AND L DOPA CARBIDOPA THERAPY IN A PATIENT WITH PARKINSONISM AND A PSYCHOTIC ILLNESS" JOURNAL OF NERVOUS AND MENTAL DISEASE, vol. 168, no. 5, 1980, pages 312-314, XP008020514 ISSN: 0022-3018 the whole document	1-3,5,6, 10-12
X	PERINI M ET AL: "BENEFIT OF FLUOPERAZINE IN DRUG-INDUCED HALLUCINATIONS DURING PARKINSON'S DISEASE MANAGEMENT" GAZZETTA MEDICA ITALIANA ARCHIVIO PER LE SCIENZE MEDICHE, vol. 148, no. 3, 1989, pages 101-104, XP008020513 ISSN: 0393-3660 abstract	1-3,5,6, 10-12

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*8\* document member of the same patent family

Date of the actual completion of the international search

29 November 2004

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Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

 International Application No  
 PCT/EP2004/005183

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	US 3 320 249 A (JACK BERNSTEIN) 16 May 1967 (1967-05-16) column 2, line 60 - line 64; claims; example 11	1,5,6, 10-12
X	US 6 482 822 B1 (AUVIN SERGE ET AL) 19 November 2002 (2002-11-19) column 1, line 40 - line 46; example 22	1,5-12
X	WO 99/07356 A (SANBERG PAUL RONALD ; SHYTLE ROLAND DOUGLAS (US); SILVER ARCHIE AAR) 18 February 1999 (1999-02-18) abstract; claims 1,5,6,8	1-6, 10-12
X	EP 0 615 749 A (UNIV VIRGINIA COMMONWEALTH) 21 September 1994 (1994-09-21) abstract	1-5,8, 10-12
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Y	US 6 057 373 A (FOGEL BARRY S) 2 May 2000 (2000-05-02) abstract column 3, line 45 - line 56 column 10, line 42 - line 46; claims	1-6, 10-12
A	"THE MERCK INDEX" 2001, MERCK & CO., INC., XP002254640 page 3780 No. 3783: Ethopropazine	1-6, 10-12
X	WO 01/78709 A (MINERVA BIOTECHNOLOGIES CORP) 25 October 2001 (2001-10-25) page 5, line 9 - page 6, line 22 * page 25, compound G *claims 1-7,35,36,41,53,55,56; figure 3	1-8, 10-12
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Intern al Application No  
PCT/EP2004/005183

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	GOTTLIEB G L ET AL: "Depot neuroleptics in the treatment of behavioral disorders in patients with Alzheimer's disease." JOURNAL OF THE AMERICAN GERIATRICS SOCIETY. UNITED STATES JUL 1988, vol. 36, no. 7, July 1988 (1988-07), pages 619-621, XP008026221 ISSN: 0002-8614 the whole document	1-5,7, 10-12
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X	WO 02/22611 A (MORTIMORE MICHAEL ; KNEGTEL RONALD (GB); CHARRIER JEAN DAMIEN (GB); VE) 21 March 2002 (2002-03-21) abstract example 15 page 47, line 26 - page 48, line 31 claims 7-10	1,5-7, 9-12
X	WO 02/083656 A (LIBERATORE ANNE-MARIE ; BIGG DENNIS (FR); ROLLAND ALAIN (FR); HARNE) 24 October 2002 (2002-10-24) page 1, lines 1-17; claims * see in particular, page 115, lines 7-11; page 119, lines 23-26; page 124, lines 12-16 *	1,5-12
X	WO 00/32175 A (PFIZER PROD INC) 8 June 2000 (2000-06-08) page 23 page 31, line 25 - line 31; table 1 claims	1,5,7, 9-12
X	WO 01/92240 A (MCDONALD ROBERT S ; MARTIN EARL V (CA); DARVESH SULTAN (CA); MAGEE) 6 December 2001 (2001-12-06) page 6, line 15 - line 19 page 20; table 1 claims 26-31; example 18	1,5,7, 10-12
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Interr, al Application No  
PCT/EP2004/005183

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DAVIS J L ET AL: "PERIPHERAL DIABETIC NEUROPATHY TREATED WITH AMITRIPTYLINE AND FLUPHENAZINE" JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, vol. 238, no. 21, 1977, pages 2291-2292, XP008026211 ISSN: 0098-7484 the whole document	1-5,8, 10-12
X	MOSLEY C A ET AL: "CONTROL OF DIABETIC NEUROPATHIC PAIN BY AMITRIPTYLINE AND FLUPHENAZINE IN MILD RENAL FAILURE" KIDNEY INTERNATIONAL, vol. 21, no. 1, 1982, page 155, XP008026206 MEETING OF THE AMERICAN SOCIETY OF NEPHROLOGY, WASHINGTON, D.C., USA, NOV. 22-24, 1981. KIDNEY INT. ISSN: 0085-2538 the whole document	1-5,8, 10-12
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X	GOMEZ-PEREZ F J ET AL: "NORTRIPTYLINE AND FLUPHENAZINE IN THE SYMPTOMATIC TREATMENT OF DIABETIC NEUROPATHY A DOUBLE-BLIND CROSS-OVER STUDY" PAIN, vol. 23, no. 4, 1985, pages 395-400, XP008026204 ISSN: 0304-3959 the whole document	1-5,8, 10-12
X	BATTLA H ET AL: "Clinical trial of amitriptyline and fluphenazine in diabetic peripheral neuropathy." SOUTHERN MEDICAL JOURNAL. UNITED STATES APR 1981, vol. 74, no. 4, April 1981 (1981-04), pages 417-418, XP008026223 ISSN: 0038-4348 the whole document	1-5,8, 10-12

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## INTERNATIONAL SEARCH REPORT

Intern<sub>l</sub> Application No  
PCT/EP2004/005183

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03/062232 A (SCRAS ;DOLO CHRISTINE (FR); CHABRIER DE LASSAUNIERE PIERRE (FR); H) 31 July 2003 (2003-07-31) page 17, line 10 - line 15; claims 1,7,11-13; example 14 page 5, line 7 - line 25 -----	1,5-12
P,X	WO 03/062388 A (UNIV CALIFORNIA) 31 July 2003 (2003-07-31) paragraph '0041! page 29; claims 1-5; figure 3 -----	1-3,5-7, 10-12

## INTERNATIONAL SEARCH REPORT

ational application No.  
PCT/EP2004/005183

### Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-5 (partly), 6 ,10-12 (partly)

Use of piperazine phenothiazine derivatives in the  
manufacture of a medicament for treating Parkinson's disease  
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2. claims: 1-5 (partly), 7, 10-12 (partly)

Use of piperazine phenothiazine derivatives in the  
manufacture of a medicament for treating Alzheimer's disease  
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3. claims: 1-5 (partly), 8, 10-12 (partly)

Use of piperazine phenothiazine derivatives in the  
manufacture of a medicament for treating peripheral  
neuropathy diseases  
---

4. claims: 1-5 (partly), 9, 10-12 (partly)

Use of piperazine phenothiazine derivatives in the  
manufacture of a medicament for treating amyotrophic lateral  
sclerosis diseases  
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/EP2004/005183

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/EP2004/005183

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## INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter-

Application No

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